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THESIS

THE SYNTHESIS OF THIOPHENE ISOLOGS OF 9,10-DIMETHYL-1,2-BENZANTHRACENE and THE SYNTHESIS OF 5-METHYL-4,7-THIONAPHTHENOQUINONE

by

Ross M Kitchen

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THE SYNTHESIS OF THIOPHENE ISOLOGS OF 9,10-DIMETHYL-1,2-BENZANTHRACENE and THE SYNTHESIS OF 5-METHYL-4,7-THIONAPHTHENEQUINONE

by

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University of Alberta.

A Thesis

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Edmonton, Alberta April, 1942

Thesis
1942
#8

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Part I

THE SYNTHESIS OF THIOPHENE ISOLOGS OF 9,10-DIMETHYL-1,2-BENZANTHRACENE

Introduction

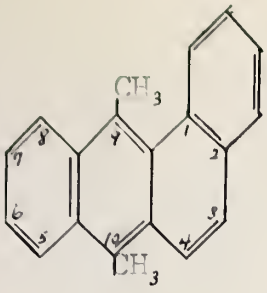
The purpose of this work was to make a further study of the 4,9-dimethyl-5,6-benzthiophanthrene(II) prepared by Sandin and Fieser(1), and to prepare the isomeric 4,9-dimethyl-7,8-benzthiophanthrene(III). The latter compound was desired so that it might be tested for carcinogenic activity. It was felt also that the work would establish with greater certainty the structure of the former compound.

In 1933 Wieland and Dane completed the degradation of desoxycholic acid to methylcholanthrene, which proved to be a potent carcinogen. Since then, hundreds of compounds have been synthesized and tested for carcinogenic activity. Several active compounds are found among the derivatives of 1,2-benzanthracene. A typical member of this group is 9,10-dimethyl-1,2-benzanthracene(I). This compound has come into use as a standard of comparison in biological tests of carcinogenicity.

The development of the cyclotron has led to the use of radioactive tracer elements in various biological fields. The knowledge that sulfur can be made radio-active and that the radioactive isotope has a fair degree of stability (half-life period of 88 days(2)) adds to the significance of sulfur-containing carcinogens. Two other points have already been mentioned by Sandin and Fieser(1), viz; the introduction of a thiophene heterocycle into a purely hydrocarbon structure should provide an interesting comparison with the original compound and secondly should cast light upon the effect of a nitrogen heterocycle which is basic as well as heterocyclic.

With these objectives in view, Sandin and Fieser(1) undertook the synthesis of a thiophene isolog of 9,10-dimethyl-1,2-benzanthracene and were successful in obtaining 4,9-dimethyl-5,6-benzthiophanthrene(II). Subsequent tests showed this compound to be a potent carcinogen(3).

In the present work the synthesis of the isomeric 4,9-dimethyl-7,8-benzthiophanthrene is described. Improved procedures for the previously prepared substance are also indicated.



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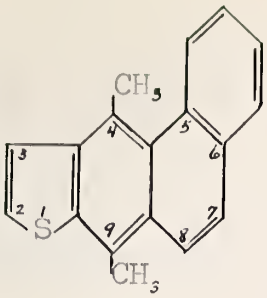

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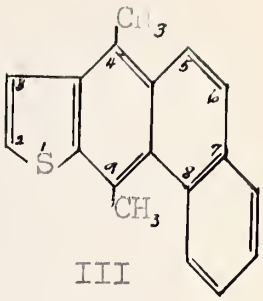

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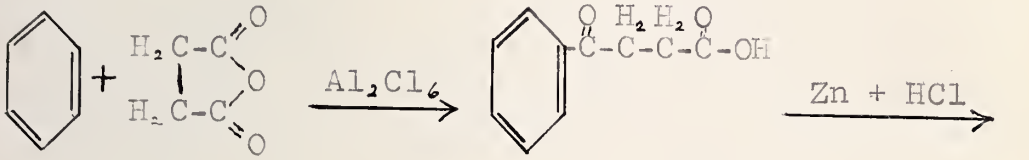
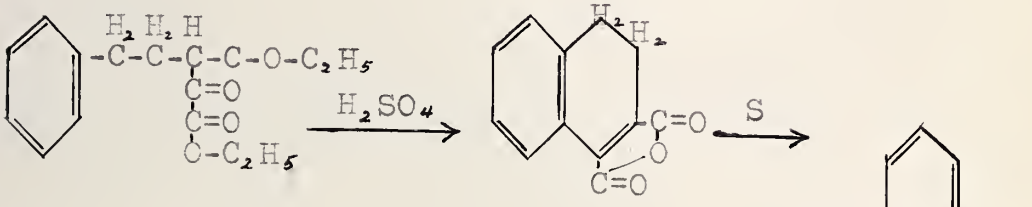
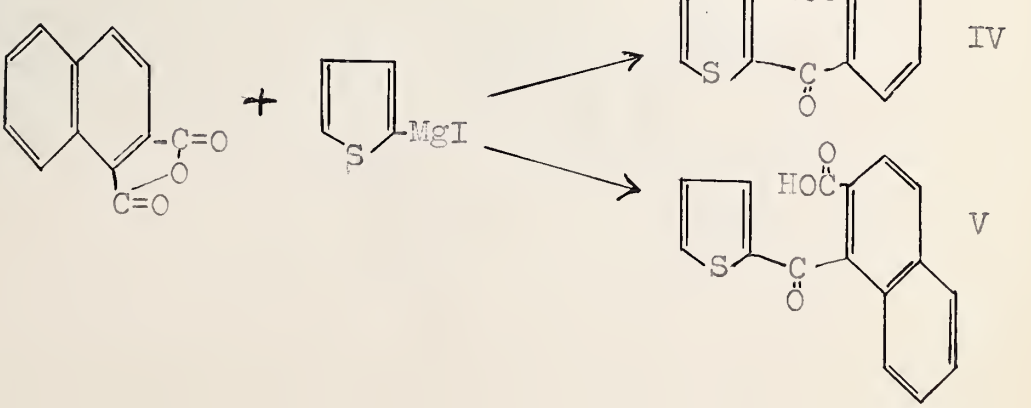
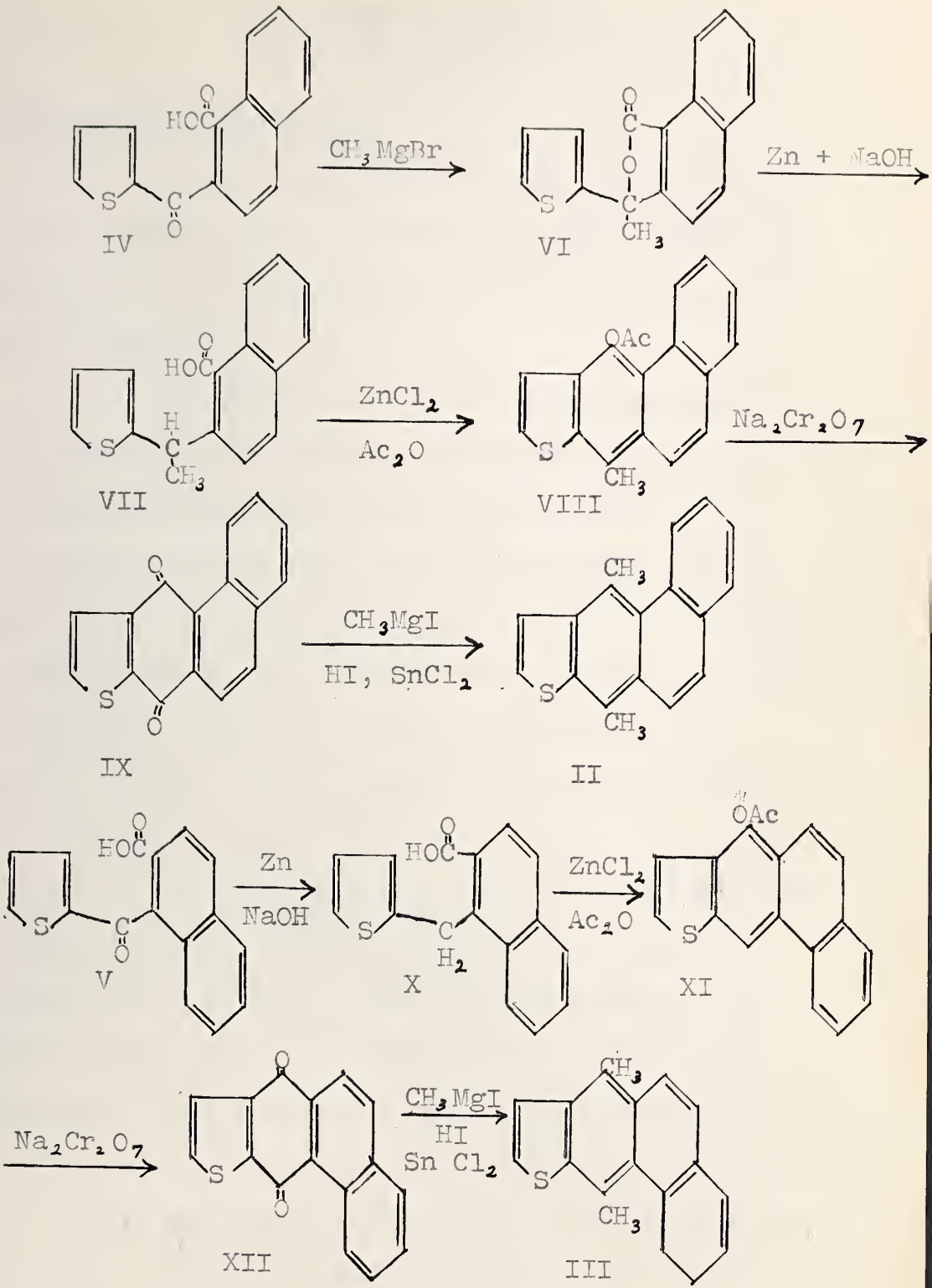






IV

V


HOC
O
S
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IV
CH3MgBr
O
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S
C
CH3
VI
Zn + NaOH
HOC
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H
C
CH3
VII
ZnCl2
Ac2O
OAc
S
CH3
VIII
Na2Cr2O7
O
S
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IX
CH3MgI
HI, SnCl2
CH3
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CH3
II
HOC
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NaOH
HOC
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X
ZnCl2
Ac2O
OAc
S
XI
Na2Cr2O7
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XII
CH3MgI
HI
Sn Cl2
CH3
S
CH3
III

Experimental Procedure

1,2-Naphthalic Anhydride:

This compound was prepared according to a series of procedures described in Organic Syntheses (4,5,6,7,8,9). The equations for the reactions are shown on page 3.

Benzene and succinic anhydride reacted in the presence of anhydrous aluminum chloride to give β-benzoylpropionic acid(4,5). The reduction of β-benzoylpropionic acid was accomplished using amalgamated zinc and hydrochloric acid(6,7), and the γ-phenylbutyric acid produced was purified by vacuum distillation. This acid was esterified(8) using absolute ethanol and concentrated sulfuric acid and the ester was vacuum distilled.

In the procedure for ester condensation(8) some modifications were introduced. The sodium was powdered under xylene in the three-necked reaction flask by the action of a mechanical stirrer of the Hershberg type(10) with a single series of loops of tantalum wire. The xylene was siphoned off, and ether and alcohol were added as described by Hershberg and Fieser(8). The ethyl oxalate (E.K.Co.) to be used was purified by washing with sodium bicarbonate

solution and redistilling. The remainder of the procedure, viz. adding ethyl oxalate, refluxing, removing ether and cyclizing, was carried out as described in the publication already mentioned.

The 3,4-dihydro-1,2-naphthalic anhydride so obtained was dehydrogenated by fusion with sulfur as described by Hershberg and Fieser(9).

Throughout this series of preparations the yields obtained were substantially the same as those recorded in the literature. In all, 110 grams of 1,2-naphthalic anhydride was prepared from 415 grams of β-benzoylpropionic acid.

Iodination of Thiophene:

Thiophene was converted to α-iodothiophene by the method of Minnis(11), using iodine and mercuric oxide. The results were not consistent, but in several of the better runs yields were obtained equal to those reported by Minnis. The product was fractionally distilled in vacuum.

Thenoylnaphthoic acids:

The Grignard reagent prepared from 3 g. of magnesium, 24 g. of α-iodothiophene and 100 ml. of anhydrous ether in an atmosphere of nitrogen was added at a moderate rate to a well-stirred solution

of 20 g. of 1,2-naphthalic anhydride in 300 ml. of dry, thiophene-free benzene. The mixture was refluxed for two hours and worked up as described by Sandin and Fieser(1). The mixture of crude acids IV and V was separated by preparing a hot saturated solution of the sodium salts and allowing it to cool. The salt of 1-thenoyl-2-naphthoic acid (V) separated as a crystalline precipitate while the salt of 2-thenoyl-1-naphthoic acid (IV) remained in solution. After filtration both salts were converted to the corresponding acids and recrystallized from acetic acid. Repeated runs gave consistently 28% yields of the acid IV melting at 158-160° and 16% yields of the acid V melting at 220-221°.

Lactone formation:

The acid IV was converted to the lactone VI according to the method of Fieser and Newman(12), varied as follows:

Three grams of magnesium was placed in a reaction flask and heated, sweeping out the air with nitrogen at the same time. After cooling, the magnesium was covered with anhydrous ether and stirred gently while methyl bromide was distilled in until the magnesium had entirely dissolved. Then a warm solution of 10 g. of the acid IV in dry, thiophene-

free benzene was allowed to run slowly into the solution of Grignard reagent. The yield of lactone melting at 112-113° was 8 grams.

An attempt to apply this method in treating the acid V proved entirely unsuccessful.

Reduction of the Lactone VI:

By the method of Newman(13), the lactone was reduced with activated zinc and sodium hydroxide. Although several runs were made, the product (VII) was not obtained in a crystalline condition as described by Sandin and Fieser(1), but invariably separated as an oil.

4-Acetoxy-9-methyl-5,6-benzthiophanthrene (VIII):

The acid VII was cyclized according to the method of Fieser and Hershberg(14) using acetic acid and acetic anhydride mixture with zinc chloride. After refluxing for an hour, the mixture was poured into water. A good yield of product melting about 185° was obtained.

5,6-Benz-4,9-thiophanthrenequinone (IX):

The acetate (VIII) (3.2 g.) was dissolved in 70 ml. of glacial acetic acid and the solution kept near the boiling point while 13 g. of

sodium dichromate (fine crystals) was added in small portions. After adding the last of the sodium dichromate, the solution was kept near boiling for one hour and allowed to stand overnight at about 60° (on top of an electric oven). It was then poured into 500 ml. of water and digested to coagulate the precipitate. The precipitate was filtered off and extracted with sodium hydroxide solution. A yield of 1.5 g. of crude material melting at 159-162° was obtained. This product was sublimed in vacuum (0.1-0.2 mm.) using a salt bath kept at 150-160° and gave 0.57 g. of pure quinone melting at 167-168°.

4,9-Dimethyl-5,6-benzthiophanthrene(II):

Following the procedure of Sandin and Fieser(1), 0.95 g. of the quinone (IX) was treated with excess methylmagnesium iodide and the solution poured into hydriodic acid and methanol. The intermediate iodomethyl compound was precipitated by adding acetic acid, filtered off, reduced with stannous chloride in dioxane and poured into water. Upon standing, the product separated in good condition. The yield was 0.7 g. (72%) of material melting at 158° with preliminary shrinking. A single recrystallization from glacial acetic acid gave material melting at 158-159°.

Reduction of the Acid V:

As already noted, the attempt to carry the acid V through the series of reactions outlined above for converting the acid IV to 4,9-dimethyl-5,6-benzthiophanthrene was unsuccessful.

As an alternative, the method of reduction used by Schoell and Neovius(15) was tried. One gram of the 1-thenoyl-2-naphthoic acid (V) was mixed with 1.5 g. of powdered zinc and refluxed for 144 hours with 32 ml. of 2N. sodium hydroxide containing 2.5 ml. of ammoniacal copper sulfate solution. After filtering, the reduced acid (X) was precipitated by adding hydrochloric acid. Attempts at crystallization proved unsuccessful, so the crude material was put through the cyclization and oxidation procedures exactly as described for the acid VII.

7,8-Benz-4,9-thiophanthrenequinone(XII):

After a single sublimation, the oxidation product melted at 204-205°. The yield was approximately 80 mg.

Two succeeding runs on 3.5 g. quantities of the acid V gave 0.46 g. and 0.67 g. of quinone(XII). In the latter case extraction of the crude product with sodium hydroxide was omitted, and the sublima-

tion proceeded even more satisfactorily than when the extraction was done. The product was identified with the "minute amount" of quinone mentioned by Sandin and Fieser(1) by a mixed melting point determination.

Anal. Calc'd for $C_{16}H_8O_2S$: S, 12.13.

Found: S, 11.92.

4,9-Dimethyl-7,8-benzthiophanthrene(III):

The quinone XII was treated in the same manner as IX. The product III did not separate as readily as its isomer II, but upon recrystallizing once from glacial acetic acid melted at 98-99°. A further recrystallization from dilute alcohol did not alter the melting point.

Trinitrobenzene was added to an alcoholic solution of III. Dark red crystals of an addition compound separated, melting at 165°.

The reduction of the lower melting keto acid IV by the method of Schoell and Neovius(15) gave an acid which did not crystallize. This product was run through the cyclization and oxidation procedures as described above. The yield of crude material melting about 150° was 2.8 g. From sublimation of this crude product 0.7 g. of material melting at 164-165.5° was obtained.

Summary

The preparation of 4,9-dimethyl-5,6-benzthiophanthrene from pure 2-thenoyl-1-naphthoic acid through the pure 5,6-benz-4,9-thiophanthrene-quinone and the preparation of 4,9-dimethyl-7,8-benzthiophanthrene from pure 1-thenoyl-2-naphthoic acid in a similar manner definitely establishes the structure of the two dimethyl compounds. The conditions used eliminate the likelihood of a rearrangement during cyclization such as that encountered by Sandin and Fieser(1).

A new compound (III) related to 9,10-dimethyl-1,2-benzanthracene has been prepared and is available for biological tests of its carcinogenic potency.

It is noteworthy that the higher melting of the two isomeric benzthiophanthrenequinones prepared gives the lower melting of the two isomeric dimethyl compounds.

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Part II

THE SYNTHESIS OF 5-METHYL-4,7-THIONAPHTHENEQUINONE

Introduction

During the past few years much investigation has been done in the Vitamin K field. The existence of a specific factor responsible for the coagulation of blood was first postulated by Henrik Dam of Copenhagen in 1935. It was not until 1939 that Vitamin K_1, the active principle from alfalfa leaves was obtained in pure form and identified as 2-methyl-3-phytyl-1,4-naphthoquinone. Since then, numerous compounds have been shown to possess Vitamin K activity. The most potent so far reported is 2-methyl-1,4-naphthoquinone(1). Of about half the potency of this latter compound, and approximately as active as Vitamin K_1 are 2-methyltetralone,3-methyltetralone, 2-methyl-1-naphthol and 3-methyl-1-naphthol(2).

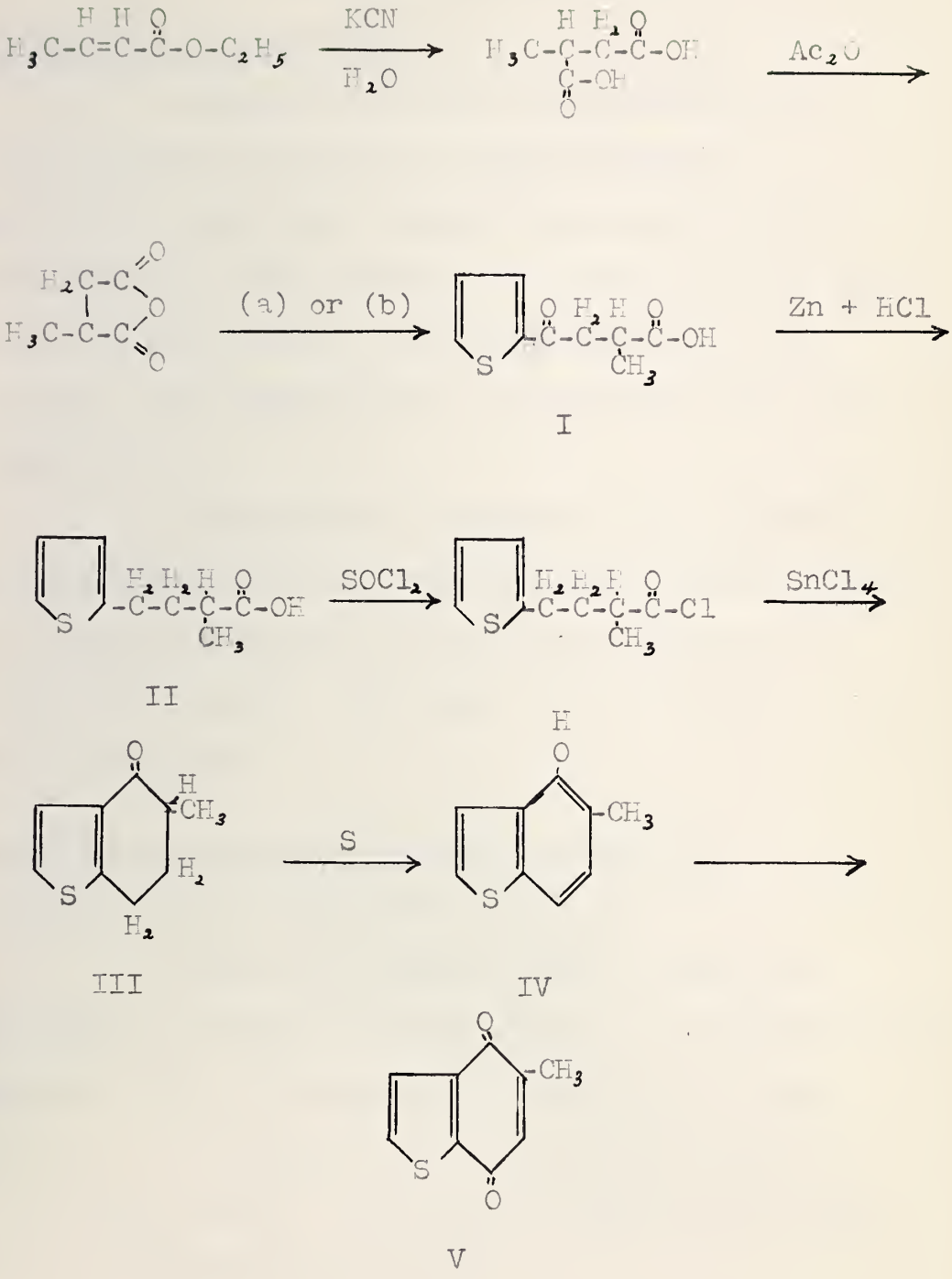
When young chicks are fed a diet containing no Vitamin K they develop a prolonged blood clotting time. Doses of a preparation to be tested for Vitamin K activity are administered orally

or intravenously to chicks thus conditioned. After a response period of eighteen hours, the blood clotting time is determined. The minimum dose required to reduce the clotting time to normal is determined. In the case of 2-methyl-1,4-naphthoquinone, the minimum effective dose is about 0.5 γ .

It has been suggested that the biological effect of these antihemorrhagic quinones may be related to their reduction potential. The present work was undertaken in order to obtain a compound similar in structure to 2-methyl-1,4-naphthoquinone but containing a heterocyclic ring in place of the benzenoid ring of the latter. With such a compound available, it should be possible to discover whether there is any correlation between antihemorrhagic activity and reduction potential.

According to Fieser and Kennelly(3) the substitution of a thiophene ring for the benzene ring of a naphthoquinone is accompanied by an increase of approximately 75 mv. in reduction potential. It will be of interest to find whether the compound synthesized in the series of reactions described below will show a similar relationship in reduction potential when compared with 2-methyl-1,4-naphthoquinone.

The steps involved in the synthesis are in general analogous to those described by Fieser and Kennelly(3) for the synthesis of 4,7-thionaphthene-quinone. The starting materials are thiophene and methylsuccinic anhydride.


KCN
H2O
Ac2O
(a) or (b)
Zn + HCl
I
SOCl2
SnCl4
II
S
III
IV
V

Experimental Procedure

Methylsuccinic Anhydride:

Methylsuccinic acid was prepared from ethyl crotonate according to Higginbotham and Lapworth(4). The yield obtained was less than that reported by the above workers. The best run gave only 228 g. of methylsuccinic acid from 250 g. of ethyl crotonate. The equations for the reactions are shown on page 17.

Methylsuccinic anhydride was prepared by refluxing methylsuccinic acid with acetic anhydride(5). The product was vacuum distilled and redistilled at atmospheric pressure. The yield was 68% of the theoretical yield.

α-Methyl-β(α'-thenoyl)-propionic acid (I):

(a) By the Friedel and Crafts synthesis-

Anhydrous aluminum chloride (115 g.) was added to a stirred mixture of 45 g. of methylsuccinic anhydride, 32 g. of thiophene and 350 ml. of nitrobenzene(3). The product was worked up and purified in the usual manner. The yield of colorless crystals melting at 110-110.5° was 3.3 g.

(b) By the Grignard synthesis-

The Grignard reagent prepared from 25 g. of iodothiophene and 3 g. of magnesium was siphoned off under nitrogen pressure and was run slowly into a well-stirred solution of 14 g. of methylsuccinic anhydride in 200 ml. of dry thiophene-free benzene. The mixture was stirred under reflux for two hours and worked up as described by Sandin and Fieser(6). The yield was 6.6 g. and the product melted at 109.5-110.5°.

Anal. Calcd. for $C_9H_{10}O_3S$: S, 16.17.

Found: S, 16.26, 16.28.

Because the Grignard synthesis proved more economical, it was used in all of the later runs. Fairly consistent results were obtained, the yield being about 28% based on iodothiophene.

α-Methyl- γ(α'-thienyl)-butyric acid (II):

Reduction of the acid I using amalgamated zinc and 1:1 hydrochloric acid at 25° (3) gave a colorless oily product, b.p. 130-135°/15 mm. Cooling the distillate to 0° gave colorless crystals which melted at 28-29°. The yield was 65-75%.

Anal. Calcd. for $C_9H_{12}O_2S$: S, 17.40

Found: S, 17.53, 17.63

4-Keto-5-methyl-4,5,6,7-tetrahydro-thionaphthene (III):

The acid II was converted to the acid chloride using thionyl chloride and pyridine in ether solution(3). The acid chloride was cyclized in carbon disulfide solution by means of anhydrous stannic chloride(3). When the steam distillate, collected after removal of the solvent, was cooled to near the freezing point, the product III separated as colorless crystals. These crystals were filtered off and purified by a second steam distillation. The yield was 30-40% based on II. The crystals melted at 35-36° when pure.

Anal. Calcd. for $C_9H_{10}OS$: S, 19.29

Found : S, 19.32, 19.36

4-Hydroxy-5-methyl-thionaphthene (IV):

The ketone III was fused with sulfur to effect dehydrogenation. The product was purified by vacuum distillation, alkali extraction and recrystallization from ligroin according to Fieser and Kennelly(3) with the omission of the second vacuum distillation. The phenol (IV) was obtained as fine colorless needles melting at 109-110°. The yield was 10-15% based on III.

Anal. Calcd. for C_9H_8OS : S, 19.52

Found : S, 19.65, 19.80

5-Methyl-4,7-thionaphthenequinone:

Following the procedure of Fieser and Fieser(7), the phenol IV was coupled with diazotised sulfanilic acid, the azo dye was reduced with sodium hydrosulfite, and the amine converted to the amine hydrochloride. The amine hydrochloride was oxidized(3) to give the quinone V. The product was filtered, washed with water, dried, and purified by sublimation under reduced pressure (100° at 15 mm.). The pure quinone formed yellow needles melting at 120-121°. The yield was 0.125 g. from 0.8 g. of IV (14.5%).

Method of Analysis:

The sulfur analyses were carried out as follows:

Into a Parr sulfur bomb (Model No. 3) were placed, in the order mentioned, 1 g. of potassium perchlorate, 15 g. (one measure) of sodium peroxide, 0.2 g. of benzoic acid, and 0.1 g. of the sample to be analysed. The bomb was closed and shaken thoroughly to mix the sample and reagents. Both the sample and reagents should be rather finely divided, though

not necessarily powdered.

The bomb was placed on the ignition plate and 3 ml. of water was poured into the recess in the cover. A hot sharp flame from a Bunsen burner was applied to the bottom of the bomb. When the water started to boil, the burner was removed and the bomb was allowed to stand for one minute, then was picked up with tongs and cooled in running water.

The bomb was opened and the fusion cup placed on its side in a 400 ml. beaker. Any material on the lower side of the cover was washed into the beaker. The beaker was covered with a watch glass, hot water was added cautiously, and the fusion was allowed to dissolve completely. The fusion cup was then removed and carefully washed.

The solution was acidified by the careful addition of 30 ml. of concentrated hydrochloric acid (litmus test). It was then filtered, diluted to about 400 ml. and while it was hot 0.2 N. barium chloride solution (about 1.5 times the calculated amount) was added to precipitate the sulfur.

After settling overnight the precipitate was filtered off in a Gooch crucible and weighed in the usual manner. From the weight of sample and weight of barium sulfate the percentage of sulfur in

the sample was calculated.

Summary

Thiophene isologs (III, IV and V) of 2-methyltetralone, 2-methyl-1-naphthol, and 2-methyl-1,4-naphthoquinone have been prepared. Tests of these heterocyclic compounds for Vitamin K activity should give an interesting series of comparisons and show the effect of substituting the less aromatic thiophene ring for a benzene ring in compounds known to possess antihemorrhagic properties. 5-Methyl-4,7-thionaphthenequinone is of particular interest since it should be possible to determine its reduction potential and thus to find whether there is any direct relationship between this property and its antihemorrhagic effect.

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